SCIENTIFIC REPORT

Short wavelength-automated perimetry compared with standard achromatic perimetry in autosomal dominant optic atrophy

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Background: Autosomal dominant optic atrophy (ADOA, Kjer-type) is a heterogeneous, non-inflammatory degeneration of retinal ganglion cells. The diagnosis of ADOA can be challenging owing to its insidious onset and large variability in phenotypic expression, both within and between individual pedigrees. The earliest literature reports relatively mild centrocaecal scotomas to white targets in ADOA, but extensive and dense peripheral field loss to coloured targets, especially blue, with Bjerrum perimetry. The phrase “inverted peripheral visual fields to coloured targets” has been used to describe this phenomenon.

Methods: Humphrey standard achromatic perimetry (SAP) and short wavelength-automated perimetry (SWAP) were carried out on five patients with ADOA.

Results: Regardless of wide variations in patient age, visual acuity, disc appearance and colour vision, the SWAP mean deviation (MD) was between 10 and 20 times more depressed than the SAP MD. The actual differences ranged from 9.38 to 13.78 dB.

Conclusions: These data are consistent with the original reports suggesting that, early in this disease process, the blue-target deficits are typically peripheral and that this difference between SAP and SWAP perimetry may be a robust indicator of ADOA in both early and late stages of this disease.

Autosomal dominant optic atrophy (ADOA, Kjer-type) is a heterogeneous, non-inflammatory degeneration of retinal ganglion cells. Although it is the most common form of inherited optic atrophy, errors in diagnosis occur often, owing to its large variability in phenotypic expression. Kjer’s¹ monograph is the foundation on which our clinical understanding of this disease rests. He studied 19 families with a total of 1176 members. Kjer tested visual fields with white test objects in 102 cases. Additionally, he had access to 39 fields provided by other clinicians. On using white target Goldmann perimetry or a tangent screen, the peripheral fields showed no defects in all but 17 patients. Centrally, Kjer found that the characteristic defect was a centrocaecal scotoma, the intensity of which varied considerably. This scotoma was “in many cases of such low intensity as to be barely detectable”.¹ Kjer’s assessment of coloured fields was, “Perception of the blue [target] was not as good as perception of the red, so that the field margins for these two colours became superimposed or inverted. In certain cases, only a remnant of the visual field for red remained nasally, while the blue was not perceived at all”.¹ Subsequently, Smith² published a review of the ADOA literature, with emphasis on Kjer’s data and his own data from three pedigrees. Smith articulated the following diagnostic criteria for ADOA:

1. Autosomal dominant inheritance.
2. Insidious onset between the ages of 4 and 8 years.
3. Moderately reduced visual acuity, 6/20–6/60.
4. Temporal pallor of the optic disc.
5. Centrocaecal enlargement of the blind spot.
6. Full peripheral fields to white targets.
7. Inverted peripheral fields to coloured targets.
8. An acquired tritan dyschromatopsia.

Of these, he believed that numbers 2, 4 and 8 were the most critical. Given Kjer’s earlier work, items 7 and 8 seem to be related (ie, the tritanopic colour vision problems seem to be consistent with a loss of sensitivity to blue targets). We asked Smith to clarify item 7. He answered, as follows:

Inverted peripheral fields to colored targets refers to the fact that, for ADOA patients, the field limits for blue targets lay within those for green targets with the red field being largest. In those days, visual fields were measured by Bjerrum screen ... or Goldman ... bowl perimeter. In healthy eyes, blue fields were largest. (Smith D, personal communication, June 2005).

Hence, the earliest studies state that peripheral visual field results using blue targets in patients with ADOA are considerably more compromised than white-target perimetry.^{1, 2} This lead these authors to the idea that Humphrey (Carl Zeiss Meditec, Dublin CA, USA) short wavelength-automated perimetry (SWAP) compared with (white on white) standard automated perimetry (SAP) might be beneficial for diagnosing ADOA in patients.

CASE STUDIES

Patient 1 was a 19-year-old Hispanic woman with a history of ADOA in her mother and maternal grandfather. Her best-corrected visual acuity (BVA) at distance was 20/80 for the right eye and 20/30 for the left eye. D-15 colour vision testing showed a single, one-place reversal in the right eye and none in the left. The right optic nerve appeared normally perfused, except for some nasal pallor. The cup/disc ratio (horizontal/vertical sync) was judged to be 0.5/0.5. The left nerve appeared normally perfused at 360°, with a cup/disc ratio of 0.4/0.4.

Patient 2 was the 51-year-old mother of patients 1 and 3. She had been previously diagnosed with ADOA and reported that her father had similar visual problems. Her BVA at distance was 20/200 OD and OS. She did not undergo any

Abbreviations: ADOA, autosomal dominant optic atrophy; BVA, best-corrected visual acuity; NTG, normal tension glaucoma; SAP, standard achromatic perimetry; SWAP, short wavelength-automated perimetry

Figure 1 The grey scale representations of the standard automated perimetry (SAP) and short wavelength-automated perimetry (SWAP) visual fields for the five cases presented here. This gestalt shows the inverted peripheral visual fields to coloured "[blue]" targets first described by Kjer¹ and amplified by Smith.² Both SAP and SWAP perimetry in the Zeiss Meditec HFAII instrument are normalised so that people without disease have clear fields without pattern defects or a reduction in the mean deviation values. The significance of these data is enhanced by the fact that each patient is serving as his or her own control.

colour vision testing. The optic nerve in the right eye appeared normally perfused with a cup/disc ratio of 0.7/0.5. The left eye had a cup/disc ratio of 0.8/0.7 and was cupped to the rim inferior temporally, with marked nerve fibre layer dropout of the inferior papillomacular bundle. The intraocular pressures were measured on three separate days and always ranged between 12 and 15 mm Hg.

Patient 3 was a 20-year-old Hispanic woman, who was by report the "unaffected" daughter of patient 2 and the sister of patient 1. Her BVA was 20/20+2 in both eyes. The right optic nerve was judged to have a cup/disc ratio of 0.5/0.5, with good colour 360°. The left eye had a cup/disc ratio of 0.7/0.7, with slight temporal pallor. D-15 colour vision testing showed no defects in either eye.

Patient 4 was a 20-year-old white man with a BVA of 20/40 in the right eye and 20/50 in the left. He had a 3-year history of reduced acuity and an "acquired" colour vision defect. He had a sister with similar problems, but neither of his parents had no known vision problems in either parent. During these 3 years, he had undergone extensive testing, including standard perimetry, electroretinography, visual-evoked response, electro-oculography, fluorescein angiography, corneal topography and a computed tomography scan. The diagnoses had ruled out "probable progressive cone dystrophy", "malingering versus optic nerve dysfunction", possible reduced acuity due to "sun gazing" and "optic atrophy in the left eye secondary to a skull fracture at the age of three." None of these stood up to scrutiny, and the patient was left with the impression that he had a problem with his optic nerve and was going blind. At this examination, the cup/disc ratios were judged to be 0.2/0.2 for the right eye and 0.3/0.3 for the left eye. Both nerves exhibited marked temporal pallor, with all other aspects of the posterior pole appearing normal. D-15 colour vision testing showed considerable tritanopic reversals in both eyes.

Patient 5 was an 18-year-old white woman and the sister of patient 4. Her BVA was 20/40+2 in the right eye and 20/40+1 in the left eye. The cup/disc ratio was judged to be 0.35, and OD and OS shallow, with temporal pallor OS>OD. D-15 colour vision testing showed a single, one-place reversal and one two-place reversal parallel to the tritan axis in the right eye and none in the left.

Summary of case studies

Figure 1 depicts SAP and SWAP grey scales for all of the visual fields. For a normal person without brunescient lenses or nerve disease, these should look similar, as they are

Figure 2 This graphical representation of the mean deviations in the short wavelength-automated perimetry and standard automated perimetry visual fields shows the large, 1–1.3 log₁₀ unit difference between the data of these two perimeter tests. The order in the first pedigree (case 1–3) was the order of examination. The propositus is case 1. Her mother with a prior diagnosis of autosomal dominant optic atrophy (ADOA) is case 2. Case 3 is the "unaffected sister" of the propositus. Cases 4 and 5 were her brother and sister.

standardised to a normal database. Figure 2 quantifies these data by plotting the mean deviation (MD) for both eyes for our five patients. There is a consistent 10–13 dB (factor of 10–20) separation between the mean data for these two tests. Note that these differences are quite consistent, despite differences in patient age, acuity, disc appearance, standard perimetry, colour vision and pedigree. The actual MD differences ranged from 9.38 to 13.78 dB, with an average difference of 11.46 dB.

DISCUSSION

Our diagnosis of ADOA was clinical, based on history and clinical testing. In the first pedigree (patients 1–3), there is a three-generation history and a longstanding diagnosis of ADOA in the mother. The patient's large cup/disc ratios suggest the possibility of glaucoma; however, glaucoma does not typically affect acuity until late in the disease process, and cupping is a well-documented sequelae of ADOA.³ In the second pedigree, two siblings presented with a similar set of symptoms consistent with ADOA, and extensive testing ruled out a host of other possibilities.

The importance of these data is not sample-size dependent. Each patient serves as his or her own control, with the statistical analysis carried out by the Humphrey instrument resident database (eg, both databases are normalised).

Newman and Biousse,⁴ in their review of inherited optic neuropathies, point out that although some authors put forward the notion that patients with ADOA manifest with tritanopia, others have shown a more generalised dyschromatopsia. Farnsworth D-15 colour vision testing was carried out on four of our five patients. Only one showed a large number of reversals in both eyes, which follow a tritan pattern. In contrast, all five of the patients tested showed an MD difference of a factor of 10 or more between standardised SWAP and SAP visual fields. Hence, these data are consistent with the historical findings that the larger tritan defect is distal to fixation—that is, "a reversal of the visual field".²

Recently, several investigators have proposed a genetic relationship between ADOA and normal tension glaucoma (NTG).^{5–10} The clinical parallels are interesting. NTG and ADOA often manifest with caecocentral field loss to SAP testing, and both conditions show cupping without increased intraocular pressure. Our data show a 1–1.3 log₁₀ unit (10–20 times) difference between SWAP and SAP visual fields for ADOA, but as yet there appear to be no published data on SWAP visual fields in patients with NTG with or without OPA1 polymorphisms.^{7–3} Our data suggest that SWAP versus SAP testing should be explored in patients with NTG, as it may have the potential for differentiating patients with NTG with and without OPA1 polymorphism.⁶

We look forward to SWAP versus SAP visual field testing being carried out on a larger population of patients with ADOA to further test its diagnostic value. We are also keenly interested in this paradigm's possible potential for differentiating patients with NTG with and without OPA1 polymorphism.⁶

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